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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/508,254	10/02/2000	Marc F. Charette	CIBT-P01-558	9598

28120 7590 07/11/2003

ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER

DEBERRY, REGINA M

ART UNIT	PAPER NUMBER
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1647

DATE MAILED: 07/11/2003

18

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/508,254

Applicant(s)

CHARETTE ET AL.

Examiner

Regina M. DeBerry

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 April 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13, 15-23 and 25-32 is/are pending in the application.
- 4a) Of the above claim(s) 2-10, 12 and 25-27 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 11, 13, 15-23 and 28-32 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 1-13, 15-23 and 25-32 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

Status of Application, Amendments and/or Claims

The amendment filed 15 April 2003 (Paper No. 17) has been entered in full. New claims 30-32 were added. Claims 1, 11, 13, 15-23, 28-32 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The rejections of claims 1, 11, 13 and 15-23 under 35 USC 103(a) as being unpatentable under *Lein et al.* in view of *Durbec et al.* as set forth at pages 11-12 of Office Action (27 October 2001, Paper No. 8) and maintained in Office Action (12 November 2002, Paper No. 15) is *withdrawn* in view of the amendment (15 April 2003, Paper No. 17).

Claim Rejections - 35 USC § 112, first paragraph, enablement

Claims 28-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The basis for this rejection is set forth at pages 7-9 of Office Action (27 October 2001, Paper No. 8) and maintained in Office Action (12 November 2002, Paper No. 15).

Applicant states that an *in vitro* or an *in vivo* model is sufficient to support the claimed methods, as long as there is correlation between the model and the claimed use. Applicant maintains that using cultured neural cells *in vitro* is a proper model that

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correlates with *in vivo* administration of morphogens and neurotrophic factors. Applicant contends that the Office Action provides neither scientific reasoning nor cited references to buttress its arguments, thus failing to meet the initial burden required by MPEP to support its argument of no correlation and non-enablement, or to rebut the presumption in favor of Applicants.

Applicant's arguments have been fully considered but not deemed persuasive. The instant claims are drawn to a pharmaceutical preparation for promoting the survival of mammalian neural cells and inhibiting the death or degeneration of mammalian neural cells. The specification teaches fiber outgrowth and survival in ganglia cultures *in vitro*. One skilled in the art would not accept the instant model as reasonably correlating to a pharmaceutical preparation. Contrary to Applicant's assertion, art was cited in Office Action (27 October 2001, Paper No. 8), which described the difficulties using proteins in treatments such as solubility, optimization and administration. Most importantly, art was cited that described the differences between cultured cells and their counterparts *in vivo*. The differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. This has often led to tissue culture being regarded in a rather skeptical light. Hefti (Journal of Neurobiology, 1994, IDS submitted by Applicant, reference #AM) teaches that cultures are typically derived from fetal or transformed neurons and tend to reflect developmental processes and cannot offer unequivocal prediction for responses of adult neurons. The cell culture studies are likely to produce false positives. They are most useful in narrowing down the choice of growth factors possibly effective in the adult

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nervous system *in vivo*. Effectiveness of a neurotrophic factor is tested in animal models of neurological diseases (page 1419, "rational for neurotrophic factor therapy"). The specification is not enabling for a pharmaceutical preparation for promoting the survival or inhibiting death/degeneration of mammalian neural cells comprising an OP/BMP morphogen and an GDNF or NGF neurotrophic factor.

Applicant also states that the examples explicitly disclose an effect of inhibiting neuron death or degeneration in Figure 1. Applicant states that in the absence of NGF, only about 5% of the control cells will survive after 2 days in culture. In contrast, addition of NT-3 and OP-1, or GDNF and OP-1 remarkably inhibited this cell death. Applicant cites page 22, lines 26-28. Applicant's arguments have been fully considered but not deemed persuasive. The specification states "a variety of peripheral ganglia derived from embryonic chickens were used as *a model for the induction of nerve outgrowth by OP-1*" (page 21, lines 14-19). Furthermore, death and degeneration are two different biological activities. Not only does the instant specification fail to teach the differences between the two actions, it fails to disclose experiments that would discern whether inhibition of death or degeneration occurred in a cell. Experiments such as the TUNEL assay, which determine whether a cell is going through apoptosis versus necrosis, were not employed. Hallmarks of apoptosis include cell shrinkage and condensation of the cytoplasm. The TUNEL assay shows condensation of chromatin and fragmentation of DNA, typically associated with apoptosis. The fluorescein diacetate/propidium iodide double staining procedure is another assays which were not employed. To demonstrate inhibition of death, the instant example would first need to show the percentage of cells

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going through apoptosis or necrosis then show that this activity was inhibited in the presence of GDNF or OP/BMP. Lastly, as was stated earlier, the specification does not teach the characteristics of degeneration of mammalian neural cells or experiments/assays to discern whether degeneration has been inhibited.

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Claim Rejections - 35 USC § 112, first paragraph, scope of enablement

Claims 1, 11, 13, 15-23 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement. The basis for this rejection is set forth at pages 5-7 of Office Action (12 November 2002, Paper No. 15).

Applicant states that the Jackowski reference, used to teach the differences between peripheral nervous system (PNS) damage and central nervous system (CNS), relates to CNS regeneration. Applicant states that a skilled artisan would readily expect that CNS neurons would behave similarly in terms of survival upon contacting the morphogen/neurotrophic factor as PNS neurons do. Applicant cites Le Roux *et al.* which demonstrate that OP-1 can stimulate dendritic outgrowth in CNS. Applicant submits Guo *et al.* and Heldin *et al.*, to demonstrate that the claimed invention is enabled for the full scope of morphogens.

Applicant's arguments have been fully considered and are deemed partly persuasive. The specification is enabling for a method for promoting survival of **mammalian peripheral ganglia *in vitro***, wherein said cell express an OP/BMP-

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activated serine/threonine kinase receptor and a GDNF- or NGF-activated tyrosine kinase receptor, comprising contacting said ganglia with an effective concentration of a preparation comprising

a) an OP/BMP morphogen having an amino acid sequence having at least 70% homology or 60% identity with the C-terminal seven cysteine skeleton of human OP-1, wherein said OP/BMP morphogen can induce ectopic bone, and

b) a GDNF neurotrophic factor or an NGF neurotrophic factor selected from GDNF, BDNF, NT-3, NT-4, NT-5 or NT-6 does not reasonably provide enablement for promoting survival of **mammalian neural cells**.

Applicant cites Le Roux *et al.*, to demonstrate that OP-1 can stimulate dendritic outgrowth in CNS neurons. However, Lein *et al.* (Int. J. Devl. Neuroscience, 1996, IDS submitted by Applicant, reference #AT) state that OP-1 does not promote dendritic growth in cultured neurons obtained from embryonic ciliary, dorsal root, trigeminal or nodose ganglia, suggesting that its morphogenetic effects are cell selective. OP-1 selectively promoted dendritic growth in adult neurons (abstract). Berkemeier *et al.* (Neuron, 1991, IDS submitted by Applicant, reference #AF) teach the inability of NT-5 to promote the survival of peripheral sensory nodose ganglion neurons but the capability of promoting the survival of sympathetic ganglion neurons (page 862).

The specification fails to demonstrate that the combination of an OP/BMP morphogen and a GDNF or NGF neurotrophic factor can promote survival of any type of neural cell. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Claim Rejections - 35 USC § 103

Claims 1, 11, 13, 15-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lein *et al.* (Int. J. Devl. Neuroscience, 1996, IDS submitted by Applicant, reference #AT) in view of Trupp *et al.* (J. Cell Biology, 1995).

Lein *et al.* teach a method comprising contacting neural cells with OP-1. Lein *et al.* teach that OP-1 induces dendritic growth. Lein *et al.* also discloses concentrations of the factors (please see reference especially abstract, the experimental procedures, figure 3, page 204, 4th paragraph, pg 212, 3rd paragraph and pg 213, 4th paragraph). Lein *et al.* does not teach the combination of OP-1 and GDNF for promoting survival or growth of neural cells.

Trupp *et al.* teach that GDNF promotes the survival of embryonic chick sympathetic neurons, embryonic chick nodose ganglion and embryonic sensory neurons. Trupp *et al.* use .1-1000ng/ml of GDNF (abstract; page 142, Figure 7; page 13, Figure 9 and page 145, Figure 11).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Lein *et al.* and Trupp *et al.* to make and use the instant invention of a method for promoting survival of mammalian neural cells. The motivation and expected success is provided by Lein *et al.* who demonstrate the importance of OP-1 in the regulation of cytoskeletal structures of neural cells which would be important for cell signaling and maintenance. Trupp *et al.* teach that GDNF promotes the survival of neural cells in the peripheral nervous system.

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Applicant states that Lein does not teach or suggest any effect of OP/NGF in promoting survival as recited in claim 1 or in inhibiting cell death as recited in claim 29. Applicant asserts that Lein teaches away from the claimed invention by stating on page 212, last paragraph that OP-1 promotes the extension of dendrites without affecting cell survival, thus discouraging a skilled artisan from attempting to study the effects of OP-1 in promoting cell survival or inhibiting cell death, let alone its synergistic effect with neurotrophic factors in promoting cell survival.

Applicant's arguments have been fully considered but are not deemed persuasive. The rejected claims are drawn to a method for promoting survival of mammalian neural cells, wherein said cell express an OP/BMP-activated serine/threonine kinase receptor and a GDNF- or NGF-activated tyrosine kinase receptor, comprising contacting said neural cells with an effective concentration of a preparation comprising:

- a) an OP/BMP morphogen having an amino acid sequence having at least 70% homology or 60% identity with the C-terminal seven cysteine skeleton of human OP-1, wherein said OP/BMP morphogen can induce ectopic bone, and
- b) a GDNF neurotrophic factor or an NGF neurotrophic factor selected from GDNF, BDNF, NT-3, NT-4, NT-5 or NT-6, **not inhibiting cell death.**

The instant claims comprise contacting neural cells with an OP/BMP morphogen and a GDNF or NGF neurotrophic factor. The intended use is promoting survival. Lein *et al.* teach a method comprising contacting neural cells with OP-1. Lein states that

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OP-1 promotes the extension of dendrites without affecting cell survival. Lein does not state that OP-1 negatively affects survival. The statement does not teach away from using OP-1 **or** OP-1 **and** a GDNF or NGF neurotrophic factor for promoting cell survival. Furthermore, the instant claims are drawn to a *combination* of OP/BMP and a GDNF or NGF. The example disclosed in the instant specification does not demonstrate cell survival with OP-1 alone (Figure 1). Lein *et al.* teach that OP-1 induces dendritic growth. One would be motivated to use OP-1 because dendritic growth would positively affect neural survival. Cell morphological and cytoskeletal structures are important features for continued existence in the cell.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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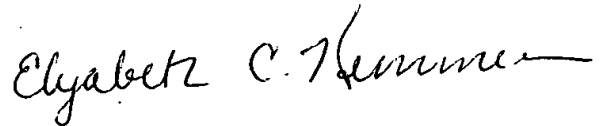
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on 9:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



RMD
July 8, 2003



ELIZABETH KEMMERER
PRIMARY EXAMINER